Brønsted acid catalysed enantioselective Biginelli reaction

Journal Name

ARTICLE

Brønsted acid catalysed green and enantioselective Biginelli reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Margherita Barbero,[a] Silvano Cadamuro[a] and Stefano Dughera*

A chiral derivative of 1,2-benzenedisulfonimide, namely (-)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide is herein proven to be an efficient chiral catalyst in a one pot three-component Biginelli reaction. In fact the yields of the target dihydropyrimidines were very high (25 examples; average 91%) and enantiomeric excesses were always excellent (14 examples; average 97%). Ultimately, we herein propose a sustainable procedure that ensures that the principles of Green Chemistry are met. The reaction displays a number of green benefits and advantages including the total absence of solvents, mild reaction conditions, relatively short reaction times and the stoichiometric reagent ratio. Target dihydropyrimidines are obtained in adequate purity, making further cromatographic purification unnecessary. Moreover, the chiral catalyst was easily recovered from the reaction mixture and reused, without the loss of catalytic activity.

Introduction

The Biginelli reaction, first described more than a century ago,[1a] is the one-pot, three component condensation of β-keto esters with aldehydes and ureas or thioureas, generally under acidic conditions.[1b] It affords dihydropyrimidine derivatives which have interesting pharmacological properties including antihypertensive, antiviral, antibacterial, antimalarial and many others types of activity.[1b]

Although the original reactions suffered from poor yields and limited substrate scope, the growing pharmacological importance of dihydropyrimidines has led to renewed exploration of the reaction conditions which has revealed a variety of compatible solvents (including ionic liquids) and catalysts to enhance the reaction.[1b, 2] Moreover, the scope of the Biginelli reaction has been widened with alcohols in the place of aldehydes as well as a number of alternative active hydrogen building-blocks instead of β-keto esters.[1b,2]

Interestingly, the stereogenic center greatly influences the biological activity of the dihydropyrimidines. For example, the R enantiomer of dihydropyrimidine SQ 32926 (Figure 1), an antihypertensive agent, is more potent than the S enantiomer.[3] Consequently, obtaining enantioenriched material is essential to increasing potency and application range in drugs.

Several enantioselective synthetic protocols have been developed over the years. One of the first, was reported by Zhu and coworkers in 2005,[4] over one-hundred years after discovery of the Biginelli reaction.

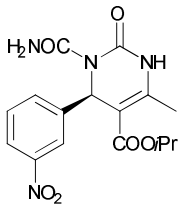


Figure 1. Antihypertensive SQ 32926

Zhu found that the use of a chiral ytterbium catalyst allowed dihydropyrimidines to be obtained in high yields and excellent enantioselectivity.

Asymmetric Biginelli reactions were then successfully carried out in the presence of chiral amines (generally with achiral Brønsted acids as co-catalysts), proline derivatives, pyrrolidinyl tetrazole, chiral ionic liquids, iodine and many others.[1b, 5]

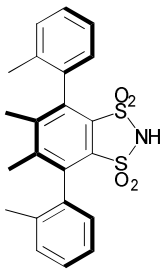
Chiral phosphoric acids[6] (and derivatives[7d]) have proven to be good chiral catalysts for Biginelli or Biginelli-like reactions which usually successfully catalysed by Brønsted acids. Target chiral dihydropyrimidines were obtained in both excellent yields and enantioselectivity.[7]

Biginelli reactions, and in general one pot multicomponent reactions, are a valid tool for build complex molecules with semplicity and brevity. In fact, they allow the formation of target products to occur in a single operation from three or more reactants, with high atom-economy and bond-forming efficiency. For these reasons, they may well be an excellent means for reaching the goal of sustainable and eco-compatible chemistry.[8]

[a] *Dipartimento di Chimica, Università di Torino, C.so Massimo d'Azeglio 48, 10125 Torino, Italy.*

Electronic Supplementary Information (ESI) available: Physical and spectroscopical data of synthesized compounds. NMR spectra. Chiral GC analyses See DOI: 10.1039/x0xx00000x

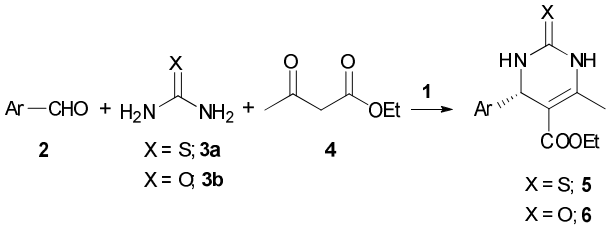
As previously highlighted, valid methods for the enantioselective Brønsted acid catalysed synthesis of dihydropyrimidines are widely known. However, these reactions are usually performed in organic solvents; catalysts are not recovered and reused and target dihydropirimidines are purified by column chromatography. The development of a Brønsted acid catalyzed green and enantioselective Biginelli protocol should therefore be of interest to many.



1

Figure 2. (-)-4,5-Dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**1**)

In light of this and in order to further enhance the chiral catalyst (-)-4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**1**; Figure 2) which is an efficient Brønsted acid chiral catalyst in Strecker[9a] and Mannich reactions,[9b] we herein report our studies into enantioselective, green Biginelli reactions between aromatic aldehydes **2**, thiourea (**3a**) or urea (**3b**) and ethyl acetoacetate (4) carried out in the presence of chiral catalyst **1** (Scheme 1).

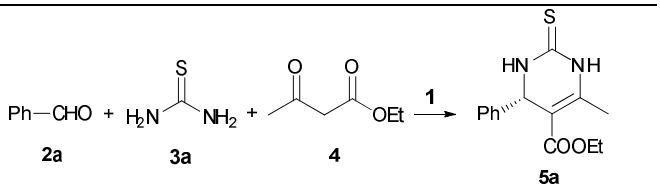


Scheme 1. Biginelli reaction catalyzed by **1**

Results and discussion

The model reaction between benzaldehyde **(2a**), thiourea (**3a**) and ethyl acetoacetate (**4**) was initially studied in the presence of a catalytic amount of **1** under varying conditions. As reported in Table 1, the best result was obtained in neat conditions, under heating at 50°C and in the presence of 5% mol of 1, which gave target **5a** in excellent yields and enantioselectivity (over 96%; Table 1; entry 8).

Table 1. Trial reactions



Entry	Solvent	**1**; mol %	Time (h)	Temp (°C)	Yield (%) of **5a** [a,b]	Ee(%)[c]
1	CH_2Cl_2	10	24	r.t.	8[d,e]	-
2	CH_2Cl_2	10	24	reflux	24[d,e]	-
3	Toluene	10	24	50	41[d,e]	-
4	Toluene	10	24	reflux	64[d,e]	-
5	H_2O	10	24	50	10[d,e]	-
6	Neat	10	24	r.t.	67[d,e]	-
7	Neat	10	3	50	97[f]	96.9
8	Neat	5	4	50	98[f]	96.4
9	Neat [g]	5	4	50	97[f]	0.3

[a] Reactants **2a**, **3a** and **4** were in equimolar amounts (0.5 mmol). [b] Yields refer to the pure **5a**. [c] Ee was determined by chiral analyses on GC connected to a column with chiral stationary phase. [d] GC-MS analyses showed the presence of starting products **2a**, **3a** and **4**. [e] In order to obtain **5a**, the crude residues were passed in a short chromatography column (EP–EtOAc, 4:1). [f] Pure **5a** (GC, GC-MS, ^{1}H-NMR) was obtained after filtering on buchner funnel and washing with a little amount of H_2O the crude residues. [g] The reaction was performed in the presence of 5 mol % of achiral 1,2-benzenedisulfonimide as a catalyst.

Moreover, catalyst **1** was easily and almost completely recovered. The recovered catalyst **1** was reused in another four consecutive reactions. Results are listed in Table 2, where it can be seen that the yields of **5a** and the enantioselectivity were consistently good over the various runs.

Table 2. Consecutive runs with recovered **1**

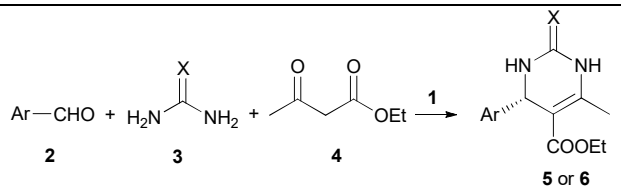
Entry	Time (h)	Yield (%) of **5a**[a,b]	Recovery (%) of **1**	Ee (%) in **5a**
1	4	98	95, 10.5 mg[c]	96.4
2	4	99	95, 10 mg[d]	96.2
3	5	95	95, 9.5 mg[e]	96.4
4	5	93	97, 9.2 mg[f]	96.3
5	5	91	97, 8.9 mg	96.4

[a] Yields refer to the pure and isolated product. [b] The reaction was performed at 50 °C with 0.5 mmol of **2a**, **3a** and **4** and 5 mol % of **1** (11 mg, 0.025 mmol). [c] Recovered **1** was used as a catalyst in entry 2. [d] Recovered **1** was used as a catalyst in entry 3. [e] Recovered **1** was used as a catalyst in entry 4. [f] Recovered **1** was used as a catalyst in entry 5.

To further exploit the generality and scope of this reaction, we reacted variously substituted aldehydes **2**, which bore either electron withdrawing or electron donating groups,with **3a** or urea (**3b**) and **4**. Good yields of target **5** and **6** were obtained regardless of the substituent electronic effect (Table 3). The influence of steric hindrance was also negligible; good yields of hindered **5b** (Table 3;

entry 2), **6a** (Table 3; entry 8) and **6e** (Table 3; entry 12) were obtained. Moreover, the enatiomeric excess was always excellent.

Table 3. Biginelli reaction between **2**, **3** and **4** catalysed by **1**



Entry	Ar in **2**	**3**	Products **5** or **6**	Time (h)	Yield (%)[a]	Ee (%) in **5** or **6**[b]
1	Ph; **2a**	**3a**	**5a**	4	98[c]	96.4
2	2-MeC_6H_4; **2b**	**3a**	**5b**	2.5	97[c]	97.8
3	3-$NO_2C_6H_4$; **2c**	**3a**	**5c**	6	94[c]	99.4
4	4-$MeOC_6H_4$; **2d**	**3a**	**5d**	2	90[c]	99.2
5	4-ClC_6H_4; **2e**	**3a**	**5e**	5	89[c]	99.1
6	4-CNC_6H_4; **2f**	**3a**	**5f**	5.5	87[c]	99.4
7	2-Thienyl; **2g**	**3a**	**5g**	3.5	94[c]	99.3
8	2-$CF_3C_6H_4$;**2h**	**3b**	**6a**	4.5	91[c]	95.6
9	3-$MeOC_6H_4$; **2i**	**3b**	**6b**	2.5	83[c]	94.7
10	4-MeC_6H_4; **2j**	**3b**	**6c**	3	97[c]	92.7
11	4-$NO_2C_6H_4$; **2k**	**3b**	**6d**	6	85[c]	93.5
12	2,4,6-$(Me)_3C_6H_2$; **2l**	**3b**	**6e**	3	97[c]	98.8
13	1-Naphthyl; **2m**	**3b**	**6f**	4.5	93[c]	98.5
14	5-Methyl-2-furyl; **2n**	**3b**	**6g**	3.5	84[c]	95.6

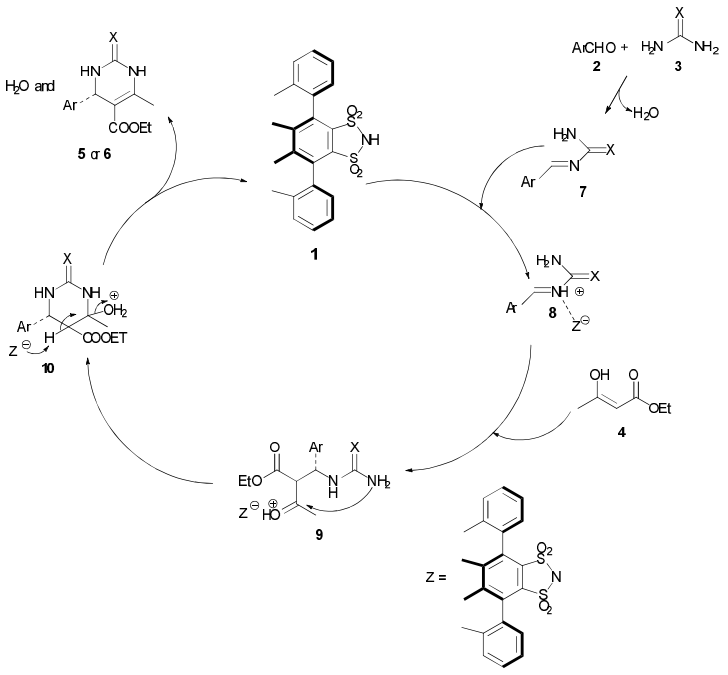
[a] The reactants **2**, **3** and **4** were in equimolar amounts (0.5 mmol). The reactions were performed at 50°C in the presence of 5 mol % of **1**. [b] Ee was determined by chiral analyses on GC connected to a column with chiral stationary phase.[c] Yields refer to the pure adducts **5** or **6** obtained after filtering on Hirsch funnel and washing with a little amount of H_2O the crude residues.

Finally, it must be stressed that, to the best of our knowledge, the use of **3b** in chiral Brønsted acid catalyzed Biginelli reactions was, until now, unknown.

In the light of these results, we can state that we have proposed a versatile, sustainable, green and convenient synthetic protocol that easily furnished adducts **5** and **6** in mild conditions. In fact, we were able to reach the following green benefits and advantages under these conditions: the total absence of solvent, mild reaction conditions, relatively short reaction times and a stoichiometric reagent ratio. Moreover, **5** and **6** were obtained with adequate purity, meaning that further cromatographic purification was unnecessary.

The easy-to handle chiral Brønsted acid catalyst **1** was advantageously used and, just like its parent 1,2-benzenedisulfonimide,[9c] turned out to be a safe, non-volatile, non-corrosive and bench-stable catalyst. A further valuable aspect of the use of **1** is its easy recovery in high yield from the reaction mixture, which it is possible thanks to its complete solubility in water, and its reuse without loss of catalytic activity in other reactions.

Since the Biginelli reaction involves the condensation of three components, this reaction can proceed down in at least five different routes, according to component reactivity.[1b] We believe that the iminium mechanism, as proposed by Folkers and Johnson[10a] and supported by the tandem-MS experiments and DFT calculations of De Sousa,[10b] is the most appropriate. In fact, the interaction between imine **7** and catalyst **1** gives rise to ion pair **8**, which is crucial to carrying out this reaction in a highly enantioselective fashion (Scheme 2).



Scheme 2. Mechanism of the Biginelli reaction catalysed by **1**

Journal Name

ARTICLE

Moreover, theoretical calculations, performed by Gong[7b] in the enantioselective Biginelli and Biginelli-like reactions catalysed by chiral phosphoric acids derivatives, confirmed the formation of an ion-pair similar to **8**.

This chiral Brønsted acid catalysed reaction may therefore be counted as an asymmetric counteranion-directed catalysis (ACDC), according to List classification.[11]

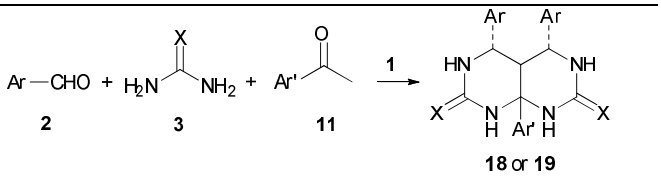
In order to expand the scope of our work, we also decided to study asymmetric Biginelli-like reactions; acetophenones **11** were reacted with selected aldehydes **2** and **3b** or **3a.** Instead of dihydropyrimidines **13** and **14**, adducts **18** and **19** were obtained in excellent yields (Scheme 3 and Table 4)

The literature shows that Biginelli-like reactions between **2**, **3** and various ketonic partners carried out with catalytic amounts of Lewis acid ($FeCl_3$)[12] or BINOL derivatives[7b] (in this specific reaction *N*-benzylthiourea was used), furnish the expected dihydropyrimidines **13, 14** or **15** (Scheme 3). On the other hand, adducts **18** have been obtained[13] by two different research groups using Biginelli-like protocol reacting aldehydes **2**, urea (**3b**) and acetophenones **11**. In the first case,[13a] mesoporous sulfated tin oxide (containing both Lewis and Brønsted acid sites) was used as the catalyst. In the second [13b] the catalyst was another Brønsted acid, $KHSO_4$. The best results were obtained in the presence of an acetic acid solvent. The reaction mechanism has recently been elucidated[13c] by DFT calculations. The results highlight the fact that protics acid are effective catalyst, as the activation energy is dramatically lower than in reactions without them.

In the light of this, we think that the hindered *N*-benzylthiourea drives the reaction towards **15**, preventing the interaction between intermediates **8** and **12** (Scheme 3; pathway b). The only possibility is therefore the cyclization of intermediate **12** (Scheme 3; pathway a).

Moreover, the nature of the acid catalyst is decisive in leading the reaction towards **13–15** or **18**,**19** (Scheme 3). Neto[14] has quite recently carried out an in depth study into the mechanisms of Lewis acid ($CuCl_2$) catalyzed Biginelli reactions. In the discussion of the reaction mechanism, he assumed that bulky intermediates, in which Cu coordinates with N atoms, would be formed. It is possible therefore that $FeCl_3$ catalyzed Biginelli-like reactions[12] fall into Neto's proposed mechanism and the bulky intermediates direct the reaction towards *pathway a*, as reported in Scheme 3

Table 4 Biginelli-like reaction between **2**, **3** and **11** catalysed by **1**



Entry	Ar in **2**	**3**	Ar' in **11**	Products **18** or **19**	Time (h)	Yield (%)[a]
1	Ph; **2a**[b]	**3b**	Ph; **11a**	-[c]	24	-
2	Ph; **2a**	**3b**	Ph; **11a**	**18a**	6	96[d]
3	4-ClC_6H_4; **2e**	**3b**	Ph; **11a**	**18b**	4	92[d]
4	4-MeC_6H_4; **2j**	**3b**	Ph; **11a**	**18c**	3.5	98[d]
5	4-CNC_6H_4; **2f**	**3b**	Ph; **11a**	**18d**	7	90[d]
6	2-MeC_6H_4; **2b**	**3b**	Ph; **11a**	**18e**	3.5	97[d]
7	3-$CF_3C_6H_4$; **2o**	**3b**	Ph; **11a**	**18f**	5.5	93[d]
8	Ph; **2a**	**3b**	4-MeC_6H_4, **11b**	**18g**	4	93[d]
9	Ph; **2a**	**3a**	Ph; **11a**	**19a**	7	81[d]
10	4-ClC_6H_4; **2e**	**3a**	Ph; **11a**	**19b**	5.5	80[d]
11	4-MeC_6H_4; **2j**	**3a**	Ph; **11a**	**19c**	4.5	89[d]
12	3-MeC_6H_4; **2p**	**3a**	Ph; **11a**	**19d**	5	88[d]

[a] The reactants **2**, **3b** and **11** were in 2: 2: 1 ratio (11 : 0.5 mmol). The reactions were performed at 50 °C in the presence of 5 mol% of **1**. [b] The reactants **2**, **3b** and **11** were in 1: 1: 1 ratio (0.5 mmol). The reactions were performed at 50°C in the presence of 5 mol% of **1** [c] GC-MS analysis of the crude residue showed a complex mixture of products. [d] Yields refer to the pure adducts **18** or **19** obtained after filtering on Hirsch funnel and washing with a little amount of H_2O the crude residues.

Adducts **18** and **19** were quite insoluble in deuterated solvents which made obtaining interpretable NMR spectra quite the challenge. Nevertheless, ^{1}H-NMR spectra (in CD_3OD) showed two clear signals: a doublet (about 4.5 ppm) and a triplet (about 3 ppm). Accordingly, we think that the *meso* form was obtained, where aryl groups (or hydrogens) are in the same positions in space. This is confirmed by the fact that their $[a]_D$ was always around 0 and that the chiral HPLC analysis of **18a** showed only one peak.

Conclusions

Scheme 3. Mechanism of Biginelli-like reaction

In this paper, a green version of asymmetric Biginelli and Biginelli-like reactions have been proposed. With respect to the reactions carried out with other chiral Brønsted acids, our conditions were able to achieve important green benefits, including the absence of solvent, complete catalyst recovery and its reuse, mild reaction conditions and relatively short reaction times. The yields of target products **5**, **6**, **18** and **19** were very high (25 exemples; average 91%) and the enantiomeric excess (14 exemples; average 97%) was excellent.

Experimental section

General remarks

Analytical grade reagents were used and reactions were monitored by GC, GC-MS. Column chromatography were performed on Merck silica gel 60 (70-230 mesh ASTM) and GF 254, respectively. Petroleum ether (PE) refers to the fraction boiling in the range 40–70 °C. Mass spectra were recorded on an HP5989B mass selective detector connected to an HP 5890 GC with a cross-linked methyl silicone capillary column. Chiral analyses were performed on a Perkin-Elmer Autosystem GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-O-methyl-6-O-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701. HPLC analysis was performed on HPLC Waters 1525 connected to a column Chiralpack IA-SFC. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Avance 200 spectrometer at 200 and 50 MHz respectively. IR spectra were recorded on a IR Perkin-Elmer UATR-two spectrometer. For the determination of optical rotations a Jasco P-2000 polarimeter was used. Chiral catalyst (-) 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**1**)[9a] and its parent o-benzenedisulfonimide[9c] were synthesized as previously reported by us. All reagents were purchased from Sigma-Aldrich or Alfa-Aesar. Structures and purity of all the products obtained in this research were confirmed by their spectral (NMR, MS, IR) data, similar to those reported in the literature. Yields and enantiomeric excesses of the pure (GC, GC-MS and NMR) isolated dihydropyrimidine-2-thiones **5** and dihydropyrimidine-2-ones **6** are reported in Table 3; yields of the pure (NMR) adducts **18** and **19** are reported in Table 4. Satisfactory microanalyses were obtained for new compounds **18d–f** and **19a–d.** Absolute configurations of the optically active **5a**,[4] **5b**,[7b] **6c**[15], **6d**[16] and **6f** [15] were determined on the basis of the measured specific rotations compared with literature values. All the other absolute configurations were assigned by analogy.

Chiral sulfonimide 1 as a catalyst in Biginelli reactions. General procedure

Chiral catalyst (-) 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**1**; 5 mol%, 11 mg, 0.025 mmol) was added to a stirring mixtures of aldehydes **2** (0.5 mmol), thiourea (**3a**) or urea (**3b**; 0.5 mmol) and **4** (0.5 mmol). The mixtures were stirred at 50 °C for the times listed in Table 3, until the GC and GC-MS analyses showed the complete disappearance of starting compounds and the complete formation of dihydropyrimidines **5** and **6**. Cold H_2O (2 ml) was added to the reaction mixture, under vigorous stirring. The resulting solids were filtered on a Hirsch funnel and washed with additional cold H_2O (2 × 1 ml) .Virtually pure (GC, GC-MS, ^{1}H NMR, ^{13}C NMR) **5** and **6** was obtained. After the above work-up, enantiomeric excesses were measured. However, in order to verify the accuracy of these measures, the crude residue of **5a,** instead of being filtered**,** was chromatographed in a short column (eluent: EP–EtOAc, 4:1) and then enantiomeric excess was determined. The values was identical (96.4% on chiral GC).

The aqueous washing was collected and evaporated under reduced pressure.Virtually pure (^{1}H NMR) (-) **1** was recovered (10.5 mg, 98% yield) and reused in other four consecutive runs as reported in Table 2.

In the same conditions a racemic mixtures of **5a** (133 mg**,** 96%) and **6e** (145 mg, 96%) were obtained using 1,2-benzenedisulfonimide as a catalyst (5 mol%, 5.5 mg, 0.025 mmol).

Chiral sulfonimide (-) 1 as a catalyst in Biginelli-like reactions. General procedure

Chiral catalyst (-) 4,5-dimethyl-3,6-bis(*o*-tolyl)-1,2-benzenedisulfonimide (**1**; 5 mol%, 11 mg, 0.025 mmol) was added to a stirring mixtures of aldehydes **2** (1 mmol), thiourea (**3a**) or urea (**3b**; 1 mmol) and **11** (0.5 mmol). The mixtures were stirred at 50 °C for the times listed in Table 4, until the TLC analyses (eluent: EP-EtOAc 3:2) showed the complete disappearance of starting compounds and the complete formation of adducts **18** and **19**. Cold H_2O (2 ml) was added to the reaction mixture, under vigorous stirring. The resulting solids were filtered on a Hirsch funnel and washed with additional cold H_2O (2 × 1 ml). Virtually pure (TLC, ^{1}H NMR) **18** and **19** were obtained.

Acknowledgements

This work was supported by Ministero dell'Università e della Ricerca and by University of Torino.

Notes and references

1 (a) P. Biginelli, *Gazz. Chim. Ital.* 1889, **19**, 212; for a thorough review see: (b) Suresh and J. S. Sandhu, *Arkivoc*, 2012, **(i),** 66 and references cited therein.

2 For recent publications see: (a) Z. Liu, R. Ma, D. Cao and C. Liu, *Molecules* 2016, **21**, 462; (b) S. Andleeb, I.-ud-Din, M. K. Rauf, S. S. Azam, A. Badshah, H. Sadaf, A. Raheel, M. N. Tahir and S. Raza, *RSC Adv.,*2016, **6**, 79651; (c) E. A. Lashmanova, V. B. Rybakov, A. K. Shiryaev, *Synthesis* 2016, **48**, 3965; (d) J. Sherwood, H. L. Parker, K. Moonen, T. J. Farmera and A. J. Hunt, *Green. Chem*., 2016, **18**, 3990; (e) C. Manikandan and K. Ganesan, *Synlett*, 2016, **27**, 1527; (f) Z. Lim, P. J. Duggan, S. S. Wan, G. Lessene, A. G. Meyer and K. L. Tuck, *Tetrahedron,* 2016, **72**, 1151.

3 K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806.

4 Y. Huang , F. Yang and C. Zhu, *J. Am. Chem. Soc.*, 2005, **127**, 16386.

5 For a recent review see: (a) E. Marcantoni and M. Petrini, *Adv. Synth. Catal.*, 2016, in print; DOI: 10.1002/adsc.201600644; for recent publications see: (b) O. V. Fedorova, Y. A. Titova, A. Y. Vigorov, M. S. Toporov, O. A. Alisienok, A. N. Murashkevich, V. P. Krasnov, G. L. Rusinov and V. N. Charushin, *Catal. Lett.*, 2016, **146**, 493; (c) Z. Hang, J. Zhu, X. Lian, P. Xu, H. Yu and S. Han, *Chem. Commun.,* 2016, **52**, 80;

6 For reviews see: (a) P. S. Bhadury and Z. Sun, *Curr. Org. Chem.***,** 2014, **18**, 127; (b) J.-P. Wan, Y. Lin and Y. Liu, *Curr. Org. Chem.*, 2014, **18**, 687: (c) D. Parmar, E.Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047.

7 (a) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.*, 2006, **128**, 14802; (b) N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 15301 (c) F. Xu, D. Huang, X. Lin and Y. Wang, *Org. Biomol. Chem.*, 2012, **10**, 4467; (d) D. An, Y.-S. Fan, Y. Gao, Z.-Q. Zhu, L.-Y. Zheng and S.-Q. Zhang, *Eur. J. Org. Chem.*, 2014, 301; (e) M. Stucchi, G. Lesma, F. Meneghetti, G. Rainoldi A. Sacchetti and A. Silvani, *J. Org. Chem.*, 2016, **81**, 1877.

8 (a) S. S. Panda, P. Khanna and L. Khanna, *Curr. Org. Chem.,* 2012*,* **16**, 507; (b) for a recent publication see: J.-H. Wang, E. Zhang, G.-M. Tang, Y.-T. Wang, Y.-Z. Cui, and S. W. Ng, *J. Solid State Chem.*, 2016, **241**, 86 and references cited therein.

9 (a) M. Barbero, S. Cadamuro, S. Dughera and R. Torregrossa, *Org. Biomol. Chem.*, 2014, **12**, 3902; (b) M. Barbero, S. Cadamuro and S. Dughera, *Tetrahedron-Asymm.*, 2015, **26,** 118; (c)) M. Barbero, S. Bazzi, S. Cadamuro and S. Dughera, *Curr. Org. Chem.,* 2011*,* **15**, 576.

10 (a) K. Folkers and T. B. Johnson, *J. Am. Chem. Soc.,* 1933, **55**, 3784; (b) R. O. M. A. De Souza, E.T. da Penha, H. M. S. Milagre, S. J. Garden, P. M. Esteves, M. N. Eberlin and O. A. C. Antunes, *Chem. Eur. J.*, 2009, **15**, 9799.

11 M. Mahlau and B. List, *Angew. Chem. Int. Ed.,* 2013, **52**, 518.

12 Z.-T. Wang, L.-W. Xu, C.-G. Xia and H.-Q. Wang, *Tetrahedron Lett.*, 2004, **45**, 7951.

13 (a) R. L. Magar, Pras. B. Thorat, Prat. B. Thorat, V. V. Thorat, B. R. Patil and R. P. Pawar, *Chin. Chem. Lett.*, 2013, **24**, 1070; (b) F. Shi, R. H. Jia, X. J. Zhang, S. J. Tu, S. Yan, Y. Zhang, B. Jiang, J. Y. Zhang and C. S. Yao, *Synthesis*, 2007, 2782; (c) Q.-S. Hu, Y.-Q. He and L.-C. Li, *Asian J. Chem.,* 2016*,* **28***,* 1244.

14 L. M. Ramos, A. Y. Ponce de Leon y Tobio, M. R. dos Santos, H. C. B. de Oliveira, A. F. Gomes, F. C. Gozzo, A. L. de Oliveira and B. A. D. Neto, J*. Org. Chem*., 2012, **77**, 10184.

15 J. Xin, L. Chang, Z. Hou, D. Shang, X. Liu and X. Feng, *Chem. Eur. J.*, 2008, **14**, 3177.

16 D. Ding and C.-G. Zhao, *Eur. J. Org. Chem.*,2010, 3802.

